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Side Effects of Dextroamphetamine Therapy of Hyperactive Children

LAWRENCE M. GREENBERG, MD, *Davis, California*
SHIRLEY A. McMAHON, MD, *Marblehead, Massachusetts*
MICHAEL A. DEEM, PhD, *Washington, D.C.*

Dextroamphetamine, prescribed in the treatment of hyperactive children, was associated with significant personality deterioration in five of 26 treated cases. Discontinuance of the drug and, in some cases, substitution of others was followed by lessened symptoms of disorganization or of toxicity. In general, children being treated with psychostimulants should be kept under careful observation for untoward reactions.

DEXTROAMPHETAMINE in the treatment of hyperactivity has become increasingly widely used since its introduction in the 1930's.[1] For a time use of the drug for this purpose received little criticism because the side effects—for example, anorexia and insomnia—were generally thought to be relatively benign and usually transient. Recently, a limited number of cases of drug-associated psychosis or severe personality deterioration have been reported in children.[2-4] On the basis of our own experience, we believe these phenomena are not so rare as was previously thought. It is the purpose of this paper to report five cases of significant personality deterioration among 26 school-age hyperactive boys treated with dextroamphetamine at Children's Hospital of the District of Columbia. The children were subjects in a double blind, placebo-controlled, short-term comparative study of the effects of dextroamphetamine and two other medications on hyperactivity and associated behaviors. The dosage schedule of dextroamphetamine was prearranged but subject to reduction or termination when side effects were encountered. Medication was begun with 5 mg in the mornings and increased 5 mg every three days to a maximum level of 20 mg morning and afternoon.

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Reprint requests to: L. M. Greenberg, MD, Department of Psychiatry, University of California, Davis, School of Medicine, Davis, CA 95616.

Reports of Cases

CASE 1. The patient, seven years of age, was referred because of nervousness, decreased attention span, and increased activity at school. His mother complained of his lying, crying, temper tantrums, low frustration tolerance, overly dependent, clinging behavior, enuresis (twice a week), and running away from home. He was the third of seven children in an intact family living in a one-bedroom apartment and was clearly labeled by his father as "retarded" and his school papers characterized as "junk." His mother, the

primary caretaker, appeared to be a concerned, warm woman who was overly burdened with children and financial problems. His father, working two jobs from 6 a.m. to 9 p.m. but earning only $100 a week, was a rejecting, rather punitive man who could not tolerate the boy's crying and babyish behavior. There was a history of prematurity followed by normal developmental landmarks. A history of pica and four to five frontal headaches a month were also reported.

The patient presented as a friendly child who had difficulty understanding simple instructions. Physical findings included profound myopia, flat feet, an incurved fifth finger, equivocal plantar reflex on the right side, posturing on heel gait, and failure to perform tandem gait. The WISC full scale IQ was 63, with verbal IQ of 74 and a performance IQ of 58. The Rorschach protocol was interpreted as primitive and immature. The psychiatrist described the boy's thinking as primitive and perseverative. The patient claimed to be only five years of age and was primarily concerned that his favorite truck would be stolen by his only friend. He was classified as having a chronic brain syndrome and "healthy response." (The diagnostic classification proposed by the Group for the Advancement of Psychiatry[5] was utilized during this study.)

During the course of treatment with dextroamphetamine, the pediatrician reported observations of a transient increase in blood pressure and heart rate, as well as mild anorexia, headache, and drowsiness. At the conclusion of the eight-week treatment period, the pediatrician observed bizarre, inappropriate behavior (that is, talking to himself) on a dosage of 15 mg twice a day. There were no appreciable changes noted in school or home performance and behavior, although the patient was reportedly "quieter" and "less nervous" after taking the medication. There were a number of significant environmental changes (moving to a new home with more adequate space, starting in a new classroom with a new teacher, replacement of glasses and being injured in a fight with another youngster), but none of these changes were judged to account for the observed inappropriate behavior. WISC performance scores were noted to have improved; however, verbal responses were noted to be more perseverative. Rorschach content was judged to be bizarre and consistent with a diagnosis of borderline psychosis. The psychiatrist reported clinical deterioration, with borderline thought processes and fantasies more in evidence. The patient claimed to be five years old but would "turn 13" at his next birthday. He appeared very slow and lethargic. He spoke of wanting to displace his youngest sister in the mother's bed and of feeling "sad" all of the time. He was fearful of monsters in his dreams and reacted to the play puppets as though they were monsters. The initial diagnostic impression was changed to developmental deviation (severe), a category which was considered equivalent to borderline psychosis. With the discontinuation of medication, symptoms of disorganization became less prominent.

CASE 2. A seven-year-old boy was referred with complaints about his school behavior: He did not sit still, did not pay attention, left the classroom, and was quite disruptive. Similar behavior was described at home. In addition, a severe speech defect, which may have contributed to his being the scapegoat of the classroom, was reported. He lived with his two working parents and two-and-one-half-year-old adopted sister in a large, comfortable house. There had been a succession of babysitters and caretakers since the patient's birth. The parents had been actively seeking medical attention for him for some time and were very concerned but perhaps overly indulgent and permissive while at the same time considering "putting him away."

On review of the history it was learned that biparietal depressions of the skull had been observed by the mother at the time of birth and she also reported a neonatal feeding problem. Developmental milestones had been delayed, with walking at 18 months and speaking at two and one-half years. The patient was said to have become hyperactive at two years with no known precipitating factors.

On physical examination, right parietal depression, abnormal speech, flat feet, posturing on heel and toe gaits, and dysdiadochokinesis were noted. WISC scores were: Full scale IQ 69, verbal IQ 63, and performance IQ 82. The patient was described by the psychologist as hyperactive, impulsive, irritable and depressed. The psychiatrist noted that he was poorly related, somewhat negativistic, and fearful. Eating was a frequently mentioned concern, and his human drawing was quite primitive, the figure having dark eyes and an enormous mouth. Two diagnoses were given: (1) chronic brain syndrome, (2) neurotic disorder, marked by negativism and passive-aggressive behavior.

After eight weeks of treatment, reports from

home and school noted little change in behavior. There were no known significant environmental changes although parental concern and anger were more clearly evident. The pediatrician had noted increased heart rate, blood pressure, sweaty palms, decreased appetite and weight on a dose of 20 mg a day, and the dose then was lowered to 15 mg a day. On the final examination the patient was described as more depressed, more perseverative, and with some question of disorganization of thought processes. Both the psychologist and psychiatrist reported increased depression, with anger, withdrawal, and pronounced negativism. The psychiatrist's diagnosis was changed to one of possible character disorder. The symptoms of toxicity abated with cessation of medication.

CASE 3. A nine-year-old patient was referred from the psychiatric outpatient service with a history of hyperactivity, fighting, lying, stuttering, and nail biting. Hyperactivity was said to begin at the time he began walking. The child had been enuretic until age eight. Living with his two working parents, he shared a bedroom with his only sibling, a four-year-old girl, although he had his own room. His mother appeared to be less involved with the boy than was his father, who tutored him every evening in a basement room converted into a classroom. The mother had had excessive weight gain and gestational diabetes during pregnancy. The infant required oxygen at birth and remained in an incubator for the first 24 hours. He was a slow feeder and had frequent colic. Physical findings included one incurved fifth finger, posturing on all gaits, synkinesis, awkwardness in fine and gross motor coordination, dysdiadochokinesis, and dysrhythmia on tapping. WISC scores were: Full scale IQ 87, verbal IQ 90, and performance IQ 86. The Rorschach responses indicated a great deal of anxiety and poor impulse control. In the psychiatric interview the patient appeared immature, restless, irritable, negativistic, and excessively dependent. Concern with getting enough food was frequently verbalized. He was mildly depressed and moderately anxious. The diagnosis was chronic brain syndrome and reactive disorder, marked by chronic anxiety.

Following the treatment period, attention span and work capacity were considerably improved and he was less distractible. No significant environmental changes were noted. During the course of medication, he experienced some sleepiness and loss of appetite which subsided when the dose of dextroamphetamine was reduced to 10 mg twice a day. The pediatrician noted that he seemed to be more dependent and clinging. The Rorschach seemed qualitatively worse to a slight degree. In the psychiatric interview, the patient seemed better related and less depressed. However, a "manic-like" quality with some perserveration and disorganization of thought processes were noted. The diagnosis was unchanged.

On reduction of the dose to 5 mg twice a day side effects abated and some reduction in hyperactivity was maintained.

CASE 4. A nine-year-old boy was brought to the center because of fighting, difficulty with school routines, and hyperactivity in school. He was the oldest of three boys living with his working parents in adequate housing. Since his mother worked days and his father evenings, one parent was always available as caretaker. His mother tended to blame the school for the boy's problems and seemed somewhat uninvolved and unconcerned about him, but his father was concerned with his provocative and "immature" behavior in the home.

The medical history was unremarkable. The pediatric examination was normal except for clumsiness and dysdiadochokinesis. The patient's behavior was seen as aggressive and rude during the examination. The WISC full scale IQ was 85, and other psychological measurements were average. On psychiatric interview, the child was described as appealing, warm, well-related, although hyperactive and admittedly "nervous." It was felt that emotional disturbance was absent to mild, and the diagnosis of developmental deviation (mild) was assigned. This category might be considered equivalent to that of "minimal brain dysfunction" in other nomenclatures.

During the eight-week course of dextroamphetamine therapy, definite side effects were noted. By the end of the first week, the patient was more grouchy. On a dose of 20 mg twice a day, at the four-week visit the patient had increased blood pressure and heart rate, sleeplessness, and decreased appetite and weight. The child acted angry and said that he thought the medicine was "poison." Two weeks after the dose was decreased to 15 mg twice a day, the boy no longer complained and showed no signs of these particular side effects. However, he remained hyperactive and became increasingly negativistic and provocative. On the same dose at the eighth week, he was angry, babyish, made animal noises, and crawled into the bottom of a toy closet to disrobe. In the

psychological examination, he showed improvement in performance scores, but throughout the examination he made many stereotyped gestures and grimaces. The Rorschach protocol revealed many pathological signs including gross disorganization and mistakes in color naming. He demonstrated primitive, bizarre responses, touching and smelling the cards. Indeed, at times he attributed specific smells to particular cards or parts of cards and was very suspicious of the procedures. The psychiatric evaluation showed clear-cut deterioration with severe impulsiveness and feelings of helplessness, of being "bad," and of being picked on by others. There was evidence for more primitive thinking and inability to contain fantasies. However, as with performance tests, school grades had improved during dextroamphetamine therapy.

After the medication was discontinued, many of the symptoms subsided. A course of thioridazine (Mellaril®) was begun, with some improvement in relatedness and a decrease in hyperactivity. After a short time, increased appetite and excessive weight gain were observed. Finally methylphenidate (Ritalin®) was prescribed, with little improvement in hyperactivity. Referral for psychotherapy had been made at the end of the dextroamphetamine trial, but the family was unable to carry out the recommendation successfully.

CASE 5. The patient, aged six, was referred because of his behavior both at home and at school. His mother felt he was bored, did not concentrate, and was overactive. He cried easily and slept fitfully. He had been hyperactive since infancy. He lived with his mother, who worked since his birth, and a two-year-old sister with whom he shared a bedroom. His father had separated from the family six months before the evaluation but visited frequently and without conflict. Although the babysitter, the same one since the patient's birth, was described as "strict," the parents appeared to be too permissive and indulgent. The medical history was unremarkable, except for weekly frontal headaches and frequent nose bleeds. On examination, the child was perceived as immature, distractible, and distant. He had flat feet and a high arched palate. There was some clumsiness, and balance was only fair. He was also noted by the psychologist to be poorly related. The WISC full scale IQ was 102, with a verbal IQ of 116 and a performance IQ of 86. There were great difficulties with visual-motor skills. The psychiatrist found the patient to be only moderately well related, with poor eye contact. His thoughts were perseverative, and there were a number of hostile fantasies which were poorly controlled and led to a disruption of speech. He manifested numerous eye tics, gestures, and mannerisms when under stress and spontaneously wished to be made of metal so he would be safe if shot. He frequently knocked his head when his "brain was not thinking right." He described having thoughts that he could not "get out of his head." The diagnoses of chronic brain syndrome and reactive disorder were made although his behavior sounded borderline at times.

During treatment with dextroamphetamine, many side effects were noted, including irritability, crying, sleeplessness, dizziness, and decreased weight and appetite. The dose was never higher than 10 mg twice a day, and the physical side effects lasted only briefly. However, by eight weeks, the child appeared depressed to the pediatrician. A significant environmental change was noted: In the sixth week of treatment he moved to the father's apartment and a new school where discipline was "stricter." Behavior was reported to have become better in the home but unchanged in the classroom after the fourth week of medication. While improvement occurred on performance tasks in the psychological battery, deterioration was evident in the Rorschach responses. The child became overreactive, expansive, and very poorly controlled. The psychiatrist found him very confused, distractible, depressed, and preoccupied with aggressive fantasies. He was giggly, labile, inappropriate, and poorly related. He occasionally expressed much anger and spoke of "something wrong with my brain" and a memory problem. He was diagnosed as being borderline psychotic.

The dextroamphetamine was discontinued and chlorpromazine (Thorazine®) was given. This change was followed by improvement in behavior, integration of thought processes, and the expression of more appropriate affect.

Discussion

These cases have been presented to alert the clinician to the need for caution in prescribing the psychostimulant, dextroamphetamine, in the treatment of hyperactive children. We have been impressed with the profound influence upon personality organization which this agent may exert during treatment for hyperactivity. Since many children who are perceived as hyperactive have

emotional disorders, either of a primary or secondary order, it is necessary to be quite careful in making observations about changes in behavior, both desirable and undesirable. Extreme care should be taken to assess the underlying personality organization of patients before administering the drug, and to continue frequent reassessment of those children in whom integration of personality seems tenuous. It should be noted that other psychostimulants—for example, Ritalin—have also been implicated in causing such disturbances.[4] In our clinical experience, these severe side effects appear to have occurred with much less frequency with methylphenidate than with dextroamphetamine. However, this is only a clinical impression which has not been carefully documented.

The cause for this disorganizing influence in some patients is not clear. However, recent studies have suggested that hyperactive children may vary in their baseline level of autonomic nervous system function, and it is conceivable that further disorganization of thought processes takes place. Additional research is needed to establish the presence of such a relationship between clinical behavior and autonomic function.

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Management of Essential Tremor

I believe that the differential diagnosis of essential tremor versus parkinsonism is one that every practicing internist has probably fairly frequently faced in his practice, particularly if he has middle-aged or elderly people, as most of us do. Everyone, I think, recognizes the parkinsonian tremor and almost invariably recognizes it correctly . . . I'd like you to emphasize in your analysis of the parkinsonian patient, not so much the tremor (which is the obvious thing that grandmother recognizes and the next-door-neighbor knows what's wrong with the patient as soon as you do) but to emphasize something that in its early manifestations is more subtle, and yet, in terms of therapy, much more important . . . and that is the rigidity and slowness of muscle movement that is the earliest manifestation almost invariably of parkinsonism. This often antedates the occurrence of tremor and sometimes is far more profound, in fact, than the tremor, although the reverse also may occur. This is important because, in its early manifestations, although relatively easy to diagnose if you think to look for it, it is usually easy to miss if you don't have it in mind. And the reason that this is important from the standpoint of essential tremor is that it is the single most important distinguishing factor between the disorder "essential tremor" and the disorder "parkinsonism"; and both have absolutely different therapeutic implications.

—Oscar M. Reinmuth, MD, *Miami*

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